ANDA 74-601

DEC 19 1997

Abbott Laboratories
Attention: Chris Markos
200 Abbott Park Road
Dept. 389, Bldg. AP30
Abbott Park, IL 60064-3537

Dear Sir:

This is in reference to your abbreviated new drug application dated December 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL.

Reference is also made to your amendments dated August 22, October 15, and October 16, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dipyridamole Injection, 5 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (I.V. Persantine®, 5 mg/mL, of Boehringer Ingelheim Pharmaceuticals, Inc).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

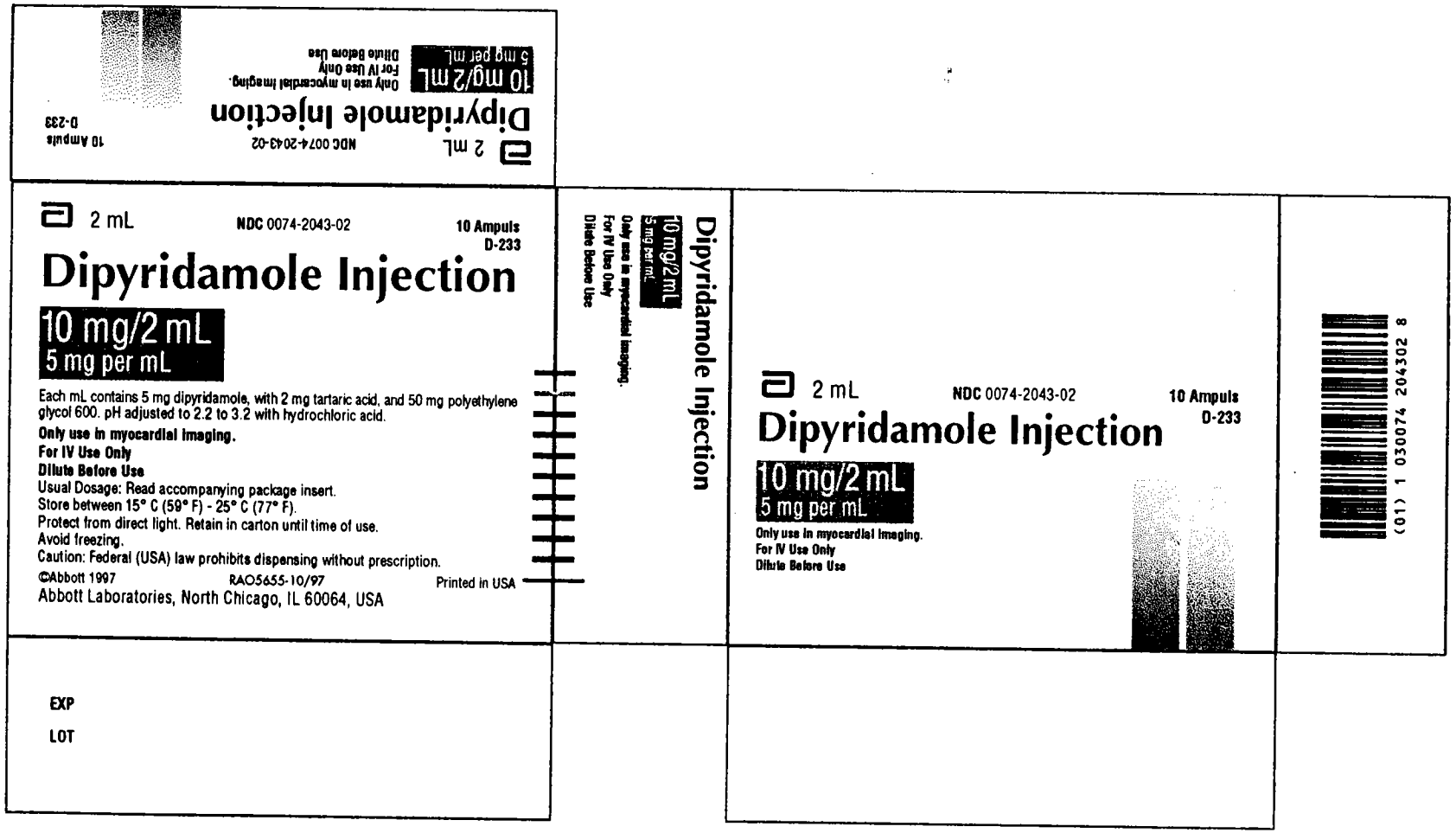
We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for 12/19/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center of Drug Evaluation and Research


2 mL
NDC 0074-2043-02
10 Ampuls
D-233
Dipyridamole Injection
10 mg/2 mL
5 mg per mL
Each mL contains 5 mg dipyridamole, with 2 mg tartaric acid, and 50 mg polyethylene glycol 600. pH adjusted to 2.2 to 3.2 with hydrochloric acid.
Only use in myocardial imaging.
For IV Use Only
Dilute Before Use
Usual Dosage: Read accompanying package insert.
Store between 15° C (59° F) - 25° C (77° F).
Protect from direct light. Retain in carton until time of use.
Avoid freezing.
Caution: Federal (USA) law prohibits dispensing without prescription.
©Abbott 1997
RAO5655-10/97
Printed in USA
Abbott Laboratories, North Chicago, IL 60064, USA
EXP
LOT
Dipyridamole Injection
10 mg/2 mL
5 mg per mL
Only use in myocardial imaging.
For IV Use Only
Dilute Before Use
(01) 1 030074 204302 8

OVERDOSAGE

No cases of overdosage in humans have been reported. It is unlikely that overdosage will occur because of the nature of use (i.e., single intravenous administration in controlled settings). See WARNINGS.

DOSAGE AND ADMINISTRATION

The dose of intravenous dipyridamole as an adjunct to thallium myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.142 mg/kg/minute (0.57 mg/kg total) infused over 4 minutes. Although the maximum tolerated dose has not been determined, clinical experience suggests that a total dose beyond 60 mg is not needed for any patient.

Prior to intravenous administration, dipyridamole injection should be diluted in at least a 1:2 ratio with sodium chloride injection, 0.45%; sodium chloride injection, 0.9%; or dextrose injection, 5% for a total volume of approximately 20 to 50 mL. Infusion of undiluted dipyridamole may cause local irritation.

Thallium-201 should be injected within 5 minutes following the 4-minute infusion of dipyridamole.

Do not mix dipyridamole injection with other drugs in the same syringe or infusion container.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Dipyridamole Injection, is available in 2 mL ampules:

10 mg/2 mL (5 mg per mL) Box of 10 (List 2043).

Store between 15° C (59° F) – 25° C (77° F).

Protect from direct light. Retain in carton until time of use.

Avoid freezing.

Caution: Federal (USA) law prohibits dispensing without prescription.

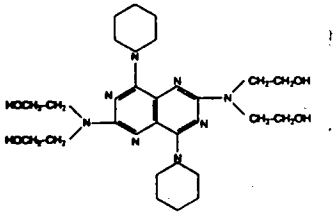
RAO5656-Rev. Oct., 1997 Printed in USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

DIPYRIDAMOLE INJECTION

For Intravenous Injection

DESCRIPTION

Dipyridamole is a coronary vasodilator described as 2,6 bis-(diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine. It has the molecular formula $C_{24}H_{40}N_8O_4$ and the following structural formula:



M. W. 504.64

Dipyridamole injection is an odorless, pale yellow liquid which can be diluted in sodium chloride injection or dextrose injection for intravenous administration.

Each mL of sterile solution for intravenous administration contains 5 mg dipyridamole, with 2 mg tartaric acid, and 50 mg polyethylene glycol 600. pH is adjusted to 2.2 to 3.2 with hydrochloric acid.

CLINICAL PHARMACOLOGY

In a study of 10 patients with angiographically normal or minimally stenosed (less than 25% luminal diameter narrowing) coronary vessels, dipyridamole in a dose of 0.56 mg/kg infused over 4 minutes resulted in an average fivefold increase in coronary blood flow velocity compared to resting coronary flow velocity (range 3.8 to 7 times resting velocity). The mean time to peak flow velocity was 6.5 minutes from the start of the 4-minute infusion (range 2.5 to 8.7 minutes). Cardiovascular responses to the intravenous administration of dipyridamole when given to patients in the supine position include a mild but significant increase in heart rate of approximately 20% and mild but significant decreases in both systolic and diastolic blood pressure of approximately 2 to 8%, with vital signs returning to baseline values in approximately 30 minutes.

Mechanism of Action: Dipyridamole is a coronary vasodilator in man. The mechanism of vasodilation has not been fully elucidated, but may result from inhibition of uptake of adenosine, an important mediator of coronary vasodilation. The vasodilatory effects of dipyridamole are abolished by administration of the adenosine receptor antagonist theophylline.

How dipyridamole-induced vasodilation leads to abnormalities in thallium distribution and ventricular function is also uncertain but presumably represents a "steal" phenomenon in which relatively intact vessels dilate, and sustain enhanced flow, leaving reduced pressure and flow across areas of hemodynamically important coronary vascular constriction.

Pharmacokinetics and Metabolism: Plasma dipyridamole concentrations decline in a triexponential fashion following intravenous infusion of dipyridamole, with half-lives averaging 3 to 12 minutes, 33 to 62 minutes, and 11.6 to 15 hours. Two minutes following a 0.568 mg/kg dose of intravenous dipyridamole administered as a 4-minute infusion, the mean dipyridamole serum concentration is 4.6±1.3 mcg/mL. The average plasma protein binding of dipyridamole is approximately 99%, primarily to α_1-glycoprotein. Dipyridamole is metabolized in the liver to the glucuronic acid conjugate and excreted with the bile. The average total body clearance is 2.3 to 3.5 mL/min/kg, with an apparent volume of distribution at steady state of 1 to 2.5 L/kg and a central apparent volume of 3 to 5 liters.

INDICATIONS AND USAGE

Dipyridamole injection is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

In a study of about 1100 patients who underwent coronary arteriography and dipyridamole injection assisted thallium imaging, the results of both tests were interpreted blindly and the sensitivity and specificity of the dipyridamole thallium study in predicting the angiographic outcome were calculated. The sensitivity of the dipyridamole test (true positive dipyridamole divided by the total number of patients with positive angiography) was about 85%. The specificity (true negative divided by the number of patients with negative angiograms) was about 50%.

OVERDOSAGE

No cases of overdosage in humans have been reported. It is unlikely that overdosage will occur because of the nature of use (i.e., single intravenous administration in controlled settings). See WARNINGS.

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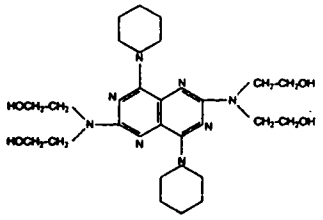

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DIVISION REVIEW SUMMARY

ANDA: 74-601

DRUG PRODUCT: Dipyridamole

FIRM: Abbott Laboratories

DOSAGE FORM: Injection

STRENGTH: 5 mg/mL

CONTAINERS: 2 cc glass ampul

CGMP STATEMENT/EIR UPDATE STATUS:
PAI was forwarded to OC on 11/18/96.

BIO INFORMATION:
The waiver from conducting in-vivo bioequivalence studies was granted by the Division of Bioequivalence, dated 8/7/95.

VALIDATION
The drug substance is a compendial article. On the other hand, the drug product is not compendial. A MV for the assay and impurities analysis were conducted and found to be acceptable.

The RLD (i.e., Persantine) and the subject drug product were submitted to stress studies by The submitted shows that these drug products have similar degradation profiles.

STABILITY
Accelerated stability (40°C) data and room temperature stability data for lot numbers EX4-224 and PD6-220 packaged in 2 cc glass ampuls are included. Both of these lots were

Lot no. PD6-219 was The release and stability data submitted for this lot shows that the drug product has significant degradation. For that reason, of the finished drug product is acceptable.

An IV diluent compatibility study was conducted and the data submitted for the different diluents show that the drug product is stable for 24 hours at room temperature.

The glass ampul is described in the container section of the application. Based on the (15 months) updated stability data submitted the proposed 15 months expiry is granted.

LABELING
Acceptable, dated 11/3/97.

STERILIZATION VALIDATION
Acceptable.

SIZE OF BIO/STABILITY BATCHES
Three lots were compounded for demonstration and stability purposes.

PROPOSED PRODUCTION BATCH
A blank manufacturing batch record for the maximum intended production batch size of s appended.

RECOMMENDATION:
Recommend approval of generic drug product Dipyridamole Injection, 5 mg/mL in 2 cc ampul.

SIGNATURE: DATE: December 3, 1997

12/10/97

Approval Summary

☛☛ * *This Approval Summary Supersedes the one dated February 11, 1997* *

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-601** Date of Submission: October 15, 1997

Applicant's Name: **Abbott Laboratories**

Established Name: **Dipyridamole Injection, 5 mg/mL**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS - 2 mL

Satisfactorily in FPL as of October 15, 1997 submission.

CARTON LABELING - 10's x 2 mL

Satisfactorily submitted on October 15, 1997 submission.

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactorily submitted on October 15, 1997 submission.

Revisions needed post-approval:

1. CONTAINER

   a. Encourage to replace "2 mL" with "2 mL Single Dose Ampul"

   b. Place the text "5 mg per mL" in the parenthesis to read "(5 mg per mL)".

2. CARTON

   See the comments under CONTAINER.

3. INSERT (HOW SUPPLIED)- First sentence:

... in 2 mL single dose ampules. [add "single dose"]

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: IV Persantine®

NDA Number: 19-817

NDA Drug Name: IV Persantine®

NDA Firm: Boehringer Ingelheim

Date of Approval of NDA Insert and supplement #:
SLR-008 approved 6/9/95 (Rev 4/95)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: IV Persantine®
Basis of Approval for the Carton Labeling: IV Persantine®

Other Comments:

The ownership of this application appears to have been transferred form Sanofi to Abbott Co. The labels and labeling submitted on October 15, 1997 reflects change of the ownership.

FOR THE RECORD:

1. MODEL LABELING - IV Persantine by Boehringer Ingelheim; revised 4/95 & approved 6/9/95. NDA 19-817/SLR-008.

2. When the New Drug Division approved this supplement (19-817/S-008) on June 9, 1995 providing for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, they requested the RLD to add at the next printing, additional serious adverse reactions (severe hypotension, anaphylaxis with laryngospasm and angioedema) to the WARNINGS section and mesenteric ischemia and infarction to the ADVERSE REACTIONS section. However, these changes were not the condition for the approval of the supplement 008 and hence, we did not ask the firm to include these changes.

3. The ownership of this application appears to have been transferred form Sanofi to Abbott Co. The labels and labeling submitted on October 15, 1997 reflects this change of the ownership.

3. INACTIVE INGREDIENTS - In a previous review, it was thought the concentrations per mL were different. The answer was that the amounts are expressed per 2 mL for the ANDA and per 1 mL for RLD, which explains why it may have looked like the ANDA was doubled. Inactives are listed on p. 101 of original submission.

4. STORAGE TEMPERATURE RECOMMENDATION -
RLD - "Store between 15°C (59°F)- 25°C (77°F). Protect from direct light. Avoid freezing."

ANDA -"Store between 15°C (59°F)- 25°C (77°F). Protect from direct light. Avoid freezing."

5. PATENTS/EXCLUSIVITIES - None.

6. PACKAGING CONFIGURATIONS

RLD - 2 mL and 10 mL ampules and 10 mL vials: All available in 5s, 10s, and 20s.

ANDA - 2 mL ampules: box of 10s

7. In an earlier NA letter that issued, the labeling comments were revised for the container and carton label. The comment to add the statement "Protect from light" on the container label was deleted. The label is too small and this information appears on the carton.

8. Bio waiver granted 8-7-95.

Date of Review: November 3, 1997 **Date of Submission: October 15, 1997**

Cycle # 4 (FPL)

Primary Reviewer: Chan Park **Date:**

Team Leader: John Grace **Date:**

1. CHEMISTRY REVIEW NO. 5

2. ANDA #74-601

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Mr. Chris Markos
200 Abbott Park Road D-389 AP30
Abbott Park, IL 60064-3537

4. BASIS OF SUBMISSION
The RLD is IV Persantine® Injection manufactured by Boehringer Ingelheim. The patent has expired and marketing exclusivity under Section 505(j)(4)(D) is not permitted.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Dipyridamole

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

December 29, 1994--	Original Submission
February 2, 1995--	Acknowledgment letter
May 16, 1995--	Deficiency letter
June 13, 1995--	Micro Review--Deficient
July 14, 1995-	Micro deficiency letter
December 15, 1995--	MV results--unacceptable. Samples were expired. New batch need to be manufactured.
May 21, 1996--	New correspondence
May 22, 1996--	New correspondence
June 5, 1996--	Amendment
October 21, 1996--	Deficiency letter
October 25, 1996-	Amendment--Micro
October 28, 1996--	Unsolicited Amendment--batch record for lot no. PD6-220 for MV samples.
November 7, 1996--	Amendment
November 20, 1996--	Telecom
December 3, 1996--	Telecom Amendment
January 10, 1997--	Correspondence
February 11, 1997--	Correspondence
April 3, 1997--	MV--acceptable with modifications
May 12, 1997--	Telephone Amendment for MV
May 15, 1997--	Telephone Amendment for MV
June 10, 1997--	Change of ownership letter
June 18, 1997--	Correspondence
July 23, 1997--	Deficiency letter (Minor)
August 22, 1997--	Amendment
October 15, 1997--	Final printed labeling amendment
October 16, 1997--	Chemistry Amendment (stability)

10. PHARMACOLOGICAL CATEGORY
Vasodilator

11. Rx or OTC
Rx

12. RELATED DMFs

13. DOSAGE FORM
Injection

14. POTENCY
5 mg/mL

15. CHEMICAL NAME AND STRUCTURE
Ethanol, 2,2',2",2"'-[(4,8-di-1-piperidinylpyrimido-[5,4-d]-pyrimidine-2,6-diyl)dinitrilo]tetrakis (Mol. weight= 504.63)

16. RECORDS AND REPORTS
None

17. COMMENTS
15 months of updated room temperature stability data for lot no. PD6-220 are appended (amendment dated 10/16/97). Based on the latest stability data submitted, and the revised degradation products specifications, the proposed 15 months expiry is granted. In addition, the MV was found satisfactory with modifications on April 21, 1997. The modifications requested by the FDA Laboratory were directly conveyed to the firm on our deficiency letter dated July 23, 1997. The firm responded to our letter on August 22, 1997, and the responses were found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
December 3, 1997

12/10/97

2/10/97

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #3
January 17, 1997

ANDA **74-601**

APPLICANT: Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

. PRODUCT NAME: **Dipyridamole Injection**

. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
5 mg/mL, 2 mL ampule,
Intravenous

. METHOD(S) OF STERILIZATION:

. PHARMACOLOGICAL CATEGORY: Vasodilator

. DATE OF INITIAL SUBMISSION: Dec 29, 1994
(Received Dec 30, 1994)

. DATE OF AMENDMENT: January 10, 1997
Subject of this Review: Telephone Amendment
(Received, January 13, 1997))

. RELATED DOCUMENTS: None

. ASSIGNED FOR REVIEW: 1/15/97

EMARKS: The amendment provides for the response to the microbiology deficiencies telefaxed, December 19, 1996.

ONCLUSIONS: This application is recommended for approval. The specific comments are provided in "E. Review Notes".

1/22/97

Andrea S. High, Ph. D.

riginal **ANDA**
uplicate ANDA
ivision Copy
ield Copy
rafted by A. High, HFD 640 x:wp\microrev\74-601a2
nitialed by F. Fang or F. Holcombe, Jr.

1/27/97

AUG 7 1995

Dipyridamole Injection
5 mg/mL, 2 mL ampule; Box of 5
ANDA # 74-601
Reviewer: Kuldeep R. Dhariwal
File Name: 74601W.D94

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016
Submission Date:
December 29, 1994

REVIEW OF A WAIVER REQUEST

The firm requests a waiver of *in vivo* bioavailability requirements for Dipyridamole Injection 5 mg/mL, 2 mL ampule under 21 CFR 320.22(b)(1)(ii). The reference listed drug is IV Persantine® (Boehringer Ingelheim, NDA # 19-817) and is available in 2 mL ampule (10 mg dipyridamole) and 10 mL ampule (50 mg dipyridamole).

FORMULATIONS:

The comparative formulations of the test and the reference products are as follows:

Ingredients	Amount (mg/mL)	
	Test	Reference (Boehringer Ingelheim)
Dipyridamole, USP	5.0	5.0
Tartaric acid, NF	2.0	2.0
Polyethylene glycol 600	50.0	50.0
Hydrochloric acid	adjust pH to 2.7 ± 0.5 finished product pH: 2.9	adjust pH to 2.7 ± 0.5
Water for injection	q.s.	q.s.

COMMENTS:

1. The drug product is for intravenous administration only.

2. The conditions of use, route of administration, and dosage form are identical to innovator product. Active and inactive ingredients are also same in test and reference listed drug.

3. The firm states that the drug product is manufactured at the McPherson, Kansas, facility, which is registered under the name Sanofi Winthrop, Inc. However, the product, when approved, will be marketed by Kanetta Pharmacal which is an affiliate of Sanofi Winthrop, Inc. The labeling included in the application reflects

the name Kanetta Pharmacal. Division of Labeling may make a note of this.

4. Labeling: Page 22, Ampule Label-Back Panel. It reads "Each mL of contains....". It should either read "Each mL contains" or "Each mL of sterile solution contains". Division of Labeling should make a note of this.

RECOMMENDATION:

The Division of Bioequivalence agrees that the information submitted by Sanofi Winthrop, Inc. demonstrates that Dipyridamole Injection 5 mg/mL, 2 mL ampule falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of the in vivo bioequivalence study requirements for the 5 mg/mL, 2 mL ampule, injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to IV Persantine^{R} 2 mL ampule containing 10 mg of dipyridamole manufactured by Boehringer Ingelheim.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED R. PATNAIK
FT INITIALED R. PATNAIK _ Date 7/6/95

Concur: _____ Date 8/2/95
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #74-601 (original), HFD-600 (Hare), HFD-630, HFD-655 (Patnaik, Dhariwal), Drug File, Division File

KRD/Draft 060695

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 907 3500

sanofi WINTHROP

DEC

MICRO/STERILITY ASSURANCE INFORMATION ENCLOSED

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Sir/Madam:

Submitted herewith in duplicate, under 21 CFR 314.50 is an original Abbreviated New Drug Application for Dipyridamole Injection, 5 mg/mL, 2 mL ampul.

Dipyridamole Injection is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 14th Edition, page 3-99. A copy appears in Section II.

The active ingredient, indications, concentration, route of administration, and conditions of use for Dipyridamole Injection, are the same as those of the innovator's product, IV Persantine®, licensed by Boehringer Ingelheim to DuPont Merck. Comparative information is attached in Section IV.

The labeling is the same in content as that of the innovator's drug IV Persantine®, except for changes that are necessary due to a change in manufacturer and editorial changes. A copy of the innovator's package insert is provided in Section V for your convenience.

The first three production batches of Dipyridamole® Injection, 5 mg/mL, 2 mL ampul, will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Furthermore, we agree to withdraw from the market any batch found to fall outside the specifications for this product.

The Sponsor of this Abbreviated New Drug Application is Sanofi Winthrop, Inc. The product is manufactured at the McPherson, Kansas, facility, which is registered under the name Sanofi Winthrop, Inc. However, the product, when approved, will be marketed by Kanetta Pharmacal which is an affiliate of Sanofi Winthrop, Inc. The labeling included in this application reflects the name Kanetta Pharmacal. There may be internal documents and correspondence to/from vendors and contract facilities that reflect the old name Sterling Winthrop Inc. and the name Sanofi Winthrop Pharmaceuticals which is an affiliate of Sanofi Winthrop, Inc. Please be aware of this when reviewing the application.

We hereby certify that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA district office, and a true copy of this original submission to the Kansas City, KS FDA district office, as per Mr. Warner's instructions.

Any inquiries concerning this Abbreviated New Drug Application should be addressed to:

Linda L. Nardone, Ph.D.
Vice President
Drug Regulatory Affairs
Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Your attention to this application is greatly appreciated.

Sincerely,

Shirley Ternyik for

Linda L. Nardone, Ph.D.
Vice President
Drug Regulatory Affairs

LLN/ST:ls

ANDA 74-601

Sanofi Winthrop, Inc.
Attention: Linda L. Nardone, Ph.D.
90 Park Avenue
New York, NY 10016

FEB 2 1995

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Dipyridamole Injection USP, 5 mg/mL, 2 mL ampule

DATE OF APPLICATION: December 29, 1994

DATE OF RECEIPT: December 30, 1994

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Consumer Safety Officer
(301) 594-1300

Sincerely yours,

2/2/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-601
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief 2/1/95 date
HFD-615/WRussell, CSC 1/25/95 date
HFD-645/BArnwine, Sup Chemist date 2/2/95
HFD-610/JPhillips, Chief LRB 2/3/95 date
WP File\russell\74\74-601
F/T bcw/1-25-95
ANDA Acknowledgement Letter!

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

sanofi WINTHROP

May 21, 1996

VIA TELEFAX AND CERTIFIED MAIL

Mr. Bill Russell, CSO (HFD-615)
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 113
Rockville, Maryland 20855-2773

CORRESPONDENCE

Subject: ANDA 74-601; Dipyridamole Injection USP, 5 mg/mL

Dear Mr. Russell:

Pursuant to our telephone conversations of May 14 and May 20, 1996, this correspondence is to confirm that Sanofi Winthrop, Inc. will respond to all the deficiencies listed in the letter to the above referenced ANDA dated May 16, 1995.

As agreed, this major amendment response will be provided to the Agency on or before June 14, 1996.

If you require any further clarification, please call me at (212) 551-4261.

Sincerely,

John Purpura
Manager CMC
Drug Regulatory Affairs

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

sanofi WINTHROP

NEW CORRESP

NC

NAE
5/31/96

May 22, 1996

VIA TELEFAX AND CERTIFIED MAIL

Mr. Bill Russell, CSO (HFD-615)
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 113
Rockville, Maryland 20855-2773

CORRESPONDENCE

Subject: ANDA 74-601; Dipyridamole Injection USP, 5 mg/mL

Dear Mr. Russell:

Pursuant to our telephone conversations of May 14 and May 20, 1996, this correspondence is to confirm that Sanofi Winthrop, Inc. will respond to all the deficiencies listed in the letter to the above referenced ANDA dated May 16, 1995.

As agreed, this major amendment response will be provided to the Agency on or before June 14, 1996 or the application will be withdrawn.

If you require any further clarification, please call me at (212) 551-4261.

Sincerely,

John Purpura
Manager CMC
Drug Regulatory Affairs

MAY 28 1996

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

sanofi WINTHROP

October 28, 1996

VIA FEDERAL EXPRESS

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

N/A

UNSOLICITED AMENDMENT

Re: ANDA 74-601; Dipyridamole Injection, 5 mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL.

Reference is also made to the October 15, 1996 correspondence from Ms. Sylvia Ricotta, Acting Supervisory Chemist, Denver District, regarding FDA's performance of method validation studies on Sanofi Winthrop's dipyridamole injection. A copy of this correspondence is included here for your convenience.

Since the samples provided to the Denver District Office were not representative of a batch previously submitted to the ANDA and in accordance with Ms. Ricotta's request, enclosed please find a copy of executed batch record PD6-220, finished product certificate of analysis for PD6-220, and representatives chromatograms of the reference standard and sample for batch PD6-220. Please note that stability data for batch PD6-220 was submitted in our amendment dated October 25, 1996.

Sanofi Winthrop Inc. hereby certifies that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director, New York FDA District Office, and a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas, FDA District Office, as per Mr. Warner's instructions.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call Mr. John Purpura, Manager CMC, at (212) 551-4261.

Sincerely,

John Purpura /for

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

sanofi WINTHROP

February 11, 1997

VIA FEDERAL EXPRESS

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AF

TELEPHONE AMENDMENT

Re: ANDA 74-601; Dipyridamole Injection, 5 mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 29, 1994 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL.

Reference is also made to our telephone conversation of February 11, 1997 with Mr. David Konigstein, Division of Labeling and Program Support, in which certain insert labeling revisions were requested. Twelve copies of revised final printed insert labeling pieces are included (six archival, six review copy).

The requested revisions included the following:

1. Under WARNINGS section, "severe hypotension, anaphylaxis with laryngospasm, and angioedema." was deleted from the first paragraph, second sentence. A period (.) was inserted after "...conduction block."

2. Under PRECAUTIONS section, "**CLINICAL PHARMACOLOGY,**" was inserted between "(see" and "**Mechanism of Action**)."

3. Under ADVERSE REACTIONS section, a ")" was inserted between "bronchospasm" and "are" in the only sentence of paragraph two. "Respiratory System" subsection heading was made boldface. The last sentence of subsection "Other" (Mesenteric ischemia and.....) was deleted.

RECEIVED
FEB 12 1997
RECEIVED
FEB 18 1997
GENERIC DRUGS
GENERIC DRUGS

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call Mr. John Purpura, Manager CMC, at (212) 551-4261.

Sincerely,

John Purpura /Ea

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

SANOFI PHARMACEUTICALS, INC.
90 PARK AVENUE
NEW YORK, NY 10016

sanofi

June 10, 1997

ANDA 74-601

NEW CORRESP
NC

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Subject: Dipyridamole Injection 5 mg/mL
ANDA 74-601

Dear Mr. Sporn:

In accordance with 21CFR 314.72(a)(1), effective June 10, 1997, Sanofi Pharmaceuticals, Inc. is transferring ownership of the manufacturing facility at 1776 North Centennial Drive, McPherson, KS 67460 and the subject ANDA to a new owner:

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-3500

Please use the above address for future correspondence.

This document consists of Confidential and/or Trade Secret Information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you have any questions, please contact Irina Privin at (212) 551-4221.

Sincerely yours,

For Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

RECEIVED
JUN 10 1997
GENERIC DRUGS

cc: Dave Guzek, Abbott Laboratories
Sandra Harder, Abbott Laboratories

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

June 18, 1997

NEW CORRESP
NC

Noted;
NDI
M. Anderson
7/29/97

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn, Director

RE: ANDA 74-601 Dipyridamole Injection, 5 mg/mL

Abbott Laboratories hereby provides notification per 21 CFR 314.72 that on June 10, 1997, a change in ownership of the subject approved application has taken place. As of that day, the ownership has been transferred from Sanofi Pharmaceuticals, New York, New York to Abbott Laboratories, North Chicago, Illinois.

Per 21 CFR 314.72(a)(2), Abbott Laboratories commits to agreements, promises, and conditions made by the former owner and has obtained and has on file, a copy of the application including supplemental applications.

Please use the address below for further correspondence:

David T. Guzek, Director HPD Regulatory Affairs
Abbott Laboratories
200 Abbott Park Road, D-389, AP30
Abbott Park, IL 60064

We trust that this information application is complete.

Sincerely,

RECEIVED
JUN 20 1997
GENERIC DRUGS

ABBOTT LABORATORIES

David T. Guzek

David T. Guzek, Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3216
FAX: (847) 938-7867

DTG/dg
g:\gms\sanofi.gms
Attachment

ABBOTT

Hospital Products Division
Abbott Laboratories
Dept. 389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

ORIG AMENDMENT FPL

October 15, 1997

10/FA

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE CORRESPONDENCE:

Final Printed Labeling

ATTENTION: Douglas Sporn
Director

Re: ANDA 74-601 Dipyridamole Injection, 5 mg/mL, 2 mL Ampul

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 29, 1994, submitted pursuant to § 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL, 2 mL fill in 2 mL ampul.

Reference is also made to the telephone call received from Kassandra Sherrod, CSO, on October 10, 1997, requesting copies of Final Printed Labeling (FPL). Contained herein please find twelve (12) copies each of FPL for the container label, carton, and package insert:

Attachment 1	Container Label
Attachment 2	Carton
Attachment 3	Package Insert

Abbott Laboratories hereby certifies that we have also sent a true copy of this Telephone Correspondence to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

If you require any clarification or further information, please call me at (847) 938-2759.

Sincerely,

ABBOTT LABORATORIES

Chris Markos

Chris Markos
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-2759
Fax: (847) 938-7867
E-Mail: markoc@hpd.abbott.com

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ABBOTT

Hospital Products Division
Abbott Laboratories
Dept. 389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

NEW CORRESP

October 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

FACSIMILE AMENDMENT

ATTENTION: Douglas Sporn
Director

Re: ANDA 74-601 Dipyridamole Injection, 5 mg/mL, 2 mL Ampul

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 29, 1994, submitted pursuant to § 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL, 2 mL fill in 2 mL ampul.

Reference is also made to the facsimile dated October 15, 1997, from Frank O. Holcombe, Jr., Ph.D., recommending that updated room temperature stability data be provided. Contained herein please find 15 month room temperature stability data for test batch PD6-220. For your convenience, a copy of the October 15, 1997 facsimile is included immediately following this letter.

Abbott Laboratories hereby certifies that we have also sent a true copy of this Facsimile Amendment to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

If you require any clarification or further information, please call me at (847) 938-2759.

Sincerely,

ABBOTT LABORATORIES

Chris Markos

Chris Markos
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-2759
Fax: (847) 938-7867
E-Mail: markoc@hpd.abbott.com

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FACSIMILE AMENDMENT

OCT 15 1997

ANDA 74-601

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT: Abbott Laboratories PHONE: 847-938-2759

ATTN: Chris Markos FAX: 847-938-7867

FROM: Kassandra Sherrod PROJECT MANAGER (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dipyridamole Injection, 5 mg/mL, 2 mL ampul.

Reference is also made to your amendment(s) dated August 22, 1997.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\fax.frm

OCT 15 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-601 APPLICANT: Abbott Labs.

DRUG PRODUCT: Dipyridamole Injection, 5 mg/mL, 2 mL ampul

The deficiency presented below represent facsimile deficiencies.

Deficiency:

The 12 months stability data submitted for lot no. PD6-220 show that significant drug product deterioration occurs as the assay value reported is reduced by At this time, we recommend that updated room temperature stability data be provided if you wish to maintain the proposed months expiry.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research